

## VI. CONCLUDING COMMENTS

Tobacco has been used in the Americas for three thousand years and its use has spread to nearly every culture in the world in the last five hundred years. Cigarette smokers puff a rod of burning tobacco and the majority of them inhale the smoke. As a consequence of smoke intake, a number of smoke constituents are absorbed and nicotine is the most active pharmacological ingredient of these compounds. Nicotine is absorbed very efficiently, enters the brain very quickly and a smoking dose is metabolised in 40 minutes which allows for brief duration of action. Smokers are sensitive to their plasma nicotine levels and they can control their intake of nicotine because of the rapidity of uptake and their perception of the moment to moment changes of nicotine level in their brain. Not only do smokers control nicotine by varying their cigarette consumption, but they control the strength of puffing to modify smoke generation, the amount of smoke retained for inhaling, and the degree of smoke inhalation for nicotine absorption. This control is more than avoidance of high toxic doses of nicotine but is an attempt to titrate for a specific nicotine dose by smoking high nicotine products less intensely and smoking low nicotine cigarettes more intensely.

The smoker's aim in titrating is obtaining an optimal dose of nicotine which will act on the body and satisfy some need. Experiments have revealed that nicotine has many actions on the body but only a very small proportion of these studies have used nicotine doses which are equivalent to smoking doses. The most consistent effect with smoking doses of nicotine is stimulation of a subset of the cholinergic neurones (ie the "nicotinic" pathways), including the autonomic nervous system and the ascending cholinergic pathways to the cortex and limbic system. The reason for this specificity of action is the similarity of the nicotine and acetylcholine molecules.

The outcome of these actions is an increase in blood levels of catecholamines and glucocorticoids and greater amounts of cortical desynchronization. All these changes are within the normal limits of the average person. Smokers believe that cigarettes alleviate mental and muscular fatigue to some extent and these effects can be attributed,

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in part, to the mobilization of energy reserves by the catecholamines and glucocorticoids. Smokers also claim that smoking helps them think and concentrate. Experimental studies with smokers have supported this claim and shown that nicotine can produce absolute enhancements in performance as well as preventing the performance decrements usually found during sustained performance. Enhanced performance of the same magnitude was found when nicotine tablets were given to non-smokers. A third important effect of nicotine is its sedative action which has been supported by questionnaire and experimental studies of smoking.

Measures of smoking behaviour during performance and while subjects are under stress show that smokers vary their nicotine intake according to the situation. In this way they obtain the required nicotine dose for stimulation or sedation depending on the situation. The rapid absorption and rapid metabolism make this substance suitable for hour-by-hour self-medication because of the personal control that can be exercised. In this respect nicotine is superior to other compounds for medication.

Nicotine taken in smoking doses seems to be relatively safe for healthy adults to use. On the evidence available at the moment it acts specifically on only a subset of the acetylcholine pathways in the body producing few side effects and none of these interfere with the normal functioning of body and mind. Even after a lifetime of use, the chronic toxicity of nicotine appears to be low. Thus nicotine stands in marked contrast to the deleterious short term and long term consequences of the socially acceptable substance, ethyl alcohol.

A number of important implications follow from these facts about nicotine. If smokers derive beneficial effects from nicotine and cigarettes are the most effective method of administering nicotine then cigarettes should be designed to deliver nicotine with minimum risk from smoke-related diseases. In my view the current trend of continuing to reduce nicotine as well as tar and carbon monoxide is not having the expected health benefits because smokers are compensating by puffing harder and inhaling more smoke. It has been argued that because compensation can only be partial with low delivery brands, intake of tar and carbon monoxide is still less than when high delivery brands were smoked and so

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these products have less risk (Rawbone, 1979). This argument would be true if cigarette consumption did not increase. However a recent paper (Wald et al, 1981) reported that over the 25 year period 1949-1974 sales-weighted average nicotine monotonically decreased. Tobacco industry figures confirm that sales-weighted nicotine monotonically decreased until 1975 from 1965, when its data were first available (RSL, 1981). In 1949, sales-weighted average nicotine was 74% higher than in 1974, representing a nicotine difference of 3.0% per annum. Over these 25 years, cigarette consumption for male smokers (RSL, 1981) increased by 50%, an average annual change of 2.0%, reflecting two-thirds compensation by consumption alone. The increase in consumption for women was even greater, as social influences contributed - it became more fashionable for females to smoke over this period. Since the mid-'70s, consumption has been affected by economic factors such as the recession and stringent tobacco taxation which make strong conclusions difficult. Nevertheless, it is intriguing that the recent downturn in consumption has coincided with a slight increase in average nicotine yield (Wald et al, 1981).

In conventional cigarette design, tar and nicotine tend to co-vary, ie low tar also entails low nicotine. Most popular cigarettes have a nicotine yield, as measured by a smoking machine, of at least 1.3 mg per cigarette, the best-selling brand having a nicotine yield of 1.6 mg per cigarette (DESS, 1981). Low tar cigarettes, however, have an average nicotine yield of only 0.7 mg per cigarette (about half popular requirement). Perhaps it is no coincidence that these low tar - low nicotine cigarettes have now, for a number of years, hovered around 15% market share - which is the same as the estimated proportion of "social smokers" (McKennell and Thomas, 1967), ie that minority group who, according to motivational researchers, smoke cigarettes for non-nicotine reasons (McKennell, 1973). For the majority of smokers, however, such low strength cigarettes are not satisfying: compensatory mechanisms became inadequate, as the effort necessary to generate required levels of nicotine is too great. A more effective approach for minimising risk and maximising benefit would be a product with medium nicotine delivery but a reduction of most other smoke components. For this concept to be acceptable, it is obviously crucial that such a cigarette also conveys sufficient flavour appeal. The Independent Scientific Committee already recognises the importance of flavour as a prerequisite for smoker satisfaction (Second Report, 1978). It is therefore essential that the product would not need to be smoked

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more intensively, or require more smoke to be inhaled, in order to satisfy taste, or to deliver the optimal amount of nicotine to the smoker. However, optimal levels of nicotine are different for different sorts of smokers. It seems to depend on such determinants as personality, sex, and average daily consumption. Thus specific types of products could be required to deliver the optimal nicotine levels for differing smoker groups.

The tobacco industry has methods for modifying smoke delivery in order to partially dissociate nicotine from tar. Some of the more drastic smoke reduction procedures change the chemical nature of the smoke (Guerin, 1980) and the toxicological implication of these shifts is unknown. Russell (1979) has briefly reported some tests of reduced tar, medium nicotine cigarettes but his comments imply that they were less acceptable than conventional products. Thus the manipulations of smoke delivery, that have been attempted so far, are very unsatisfactory, not only because they may leave harmful smoke compounds but because they remove important flavours. Clearly, future progress must be in the direction of reduction of specific smoke constituents to reduce risk but maintain flavour.

Unfortunately, we have only a limited amount of toxicological information on a few of the 4000 identified compounds in tobacco and tobacco smoke on which to base a selective reduction strategy. It is said that tobacco smoke is a relatively mild carcinogen (Tso, 1980) which means either that the hazardous compound or compounds are only weak carcinogens or the toxic compound is present in very small quantities. In the latter case the task of identification of the constituents to be reduced will be formidable.

Problems may also arise with the identification of key flavours because taste sensitivity is not uniform across the flavour spectrum. This non-uniformity means that some smoke constituents which are present in large amounts may contribute very little to smoke flavour while a trace component may be essential for a balanced sensory impact. Conceivably chemicals that are essential flavour components could also be hazardous (Second Report, 1978). In this case, non-toxic, flavour additives will have to be substituted for the desired flavour and to

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fortify the other flavours in order to preserve the characteristic full flavour impact for the smoker.

It is clear that the way to a less hazardous cigarette is not an easy one. However, the development of a medium nicotine cigarette, possibly with reduction of some smoke components, suitably enhanced with flavour, could well represent an important milestone along this path. The end of the road could not only be a safer cigarette but also a more satisfying one. Nicotine has much to commend it.

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